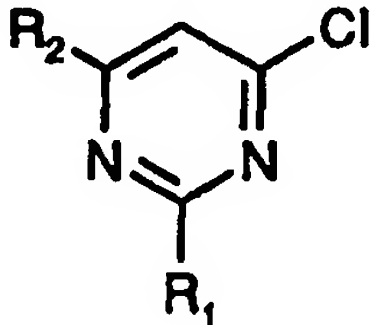
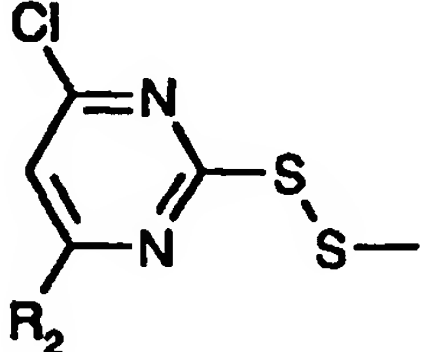
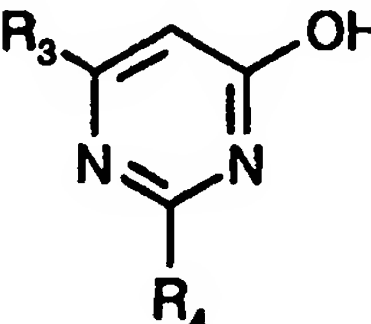


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>C07D 239/30, 239/38, 239/56, 405/12</b>		<b>A1</b>	(11) International Publication Number: <b>WO 00/46212</b>
			(43) International Publication Date: 10 August 2000 (10.08.00)
<p>(21) International Application Number: PCT/EP00/00873</p> <p>(22) International Filing Date: 3 February 2000 (03.02.00)</p> <p>(30) Priority Data: 223/99 5 February 1999 (05.02.99) CH</p> <p>(71) Applicant (for all designated States except AT US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).</p> <p>(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): URWYLER, Bernhard [CH/CH]; Im Kirsgarten 22, CH-4106 Therwil (CH). RAPOLD, Thomas [DE/CH]; Robinienweg 671, CH-4323 Wallbach (CH). PASSAFARO, Marco [CH/CH]; Weihermatt 3, CH-5082 Kaisten (CH). SEIFERT, Gottfried [CH/CH]; Muehleweg 20, CH-4312 Magden (CH).</p> <p>(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent &amp; Trademark Department, CH-4002 Basel (CH).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
(54) Title: METHOD OF PRODUCING SUBSTITUTED PYRIMIDINE DERIVATIVES			
(57) Abstract			
<p>Method of producing 4-chloropyrimidine derivatives of formula (I) wherein, R<sub>1</sub> is chlorine, CH<sub>3</sub>S- or a radical (a); and R<sub>2</sub> is chlorine or CH<sub>3</sub>O- by chlorination of a compound of formula (II), wherein R<sub>3</sub> signifies OH or CH<sub>3</sub>O-; and R<sub>4</sub> signifies OH, CH<sub>3</sub>S- or SH, in the presence of an inert solvent and at least one catalyst, as well as the use of these compounds of formula (I) in the production of 7[(4,6-dimethoxy-pyrimidin-2-yl)thio]-3-methylphthalide.</p>			
		 <p style="text-align: right;">(I)</p>	
		 <p style="text-align: right;">(a)</p>	
		 <p style="text-align: right;">(II)</p>	

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Method of producing substituted pyrimidine derivatives

The present invention relates to a new method of producing specifically substituted 4-chloropyrimidine derivatives.

In Helv. Chim. Acta 72, 744 (1989), a method of producing bis-(4,6-dichloropyrimidin-2-yl)-disulphide is described. According to this method, 2-thiobarbituric acid is reacted together with phosphorus oxychloride ( $\text{POCl}_3$ ) and N,N-diethylaniline in a ratio of 2:1, whereby the desired product is obtained in almost quantitative yield.

In J. Org. Chem. 26, 792 (1961), the production of 4,6-dichloro-2-(methylthio)pyrimidine by reacting 2-(methylthio)-4,6-pyrimidinediol and phosphorus oxychloride without solvents, and at reflux temperature, is described. The desired product is obtained in a yield of 16.6%.

J. Org. Chem. 27, 1462 (1962) describes the production of 4,6-dichloro-2-(methylthio)-pyrimidine by means of chlorination of 2-methylthio-4-chloro-6-pyrimidinol with phosphorus oxychloride in the presence of dimethylaniline.

J. Am. Chem. Soc. 76, 2899 (1954) describes the production of bis-(2,4-dimethoxy)-6-pyrimidine)disulphide starting with 2,4-dimethoxy-6-pyrimidinethiole using hydrogen peroxide in dioxane in 73% yield.

Furthermore, DE-A-4 429 466, EP-A-0 697 406 and EP-A-0 747 364 describe the production of 2,4,6-trichloropyrimidine by means of chlorination of barbituric acid, using excess phosphorus oxychloride, in the presence of a tertiary amine.

All these described methods use, as the chlorination or oxidation agents, phosphorus chlorides such as phosphorus oxychloride, phosphorus trichloride or phosphorus pentachloride or the described phosphorus chlorides in combination with chlorine or thionyl chloride as additional optimising variants, or hydrogen peroxide.

However, the yields and purities of the products obtained from these methods are frequently unsatisfactory. In addition, when using phosphorus chlorides as chlorination and oxidation agents, various phosphate salts are produced as waste material, which is a

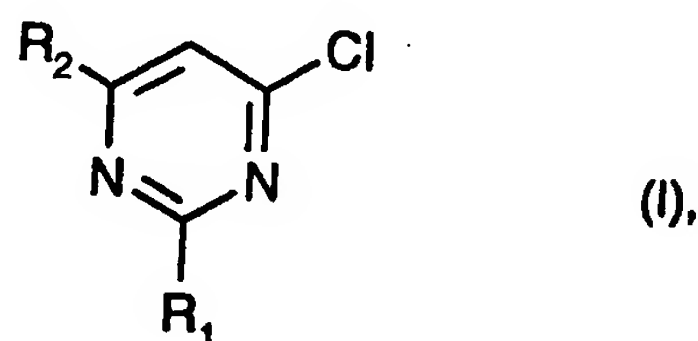
- 2 -

problem in respect of large-scale production methods, especially from an ecological point of view.

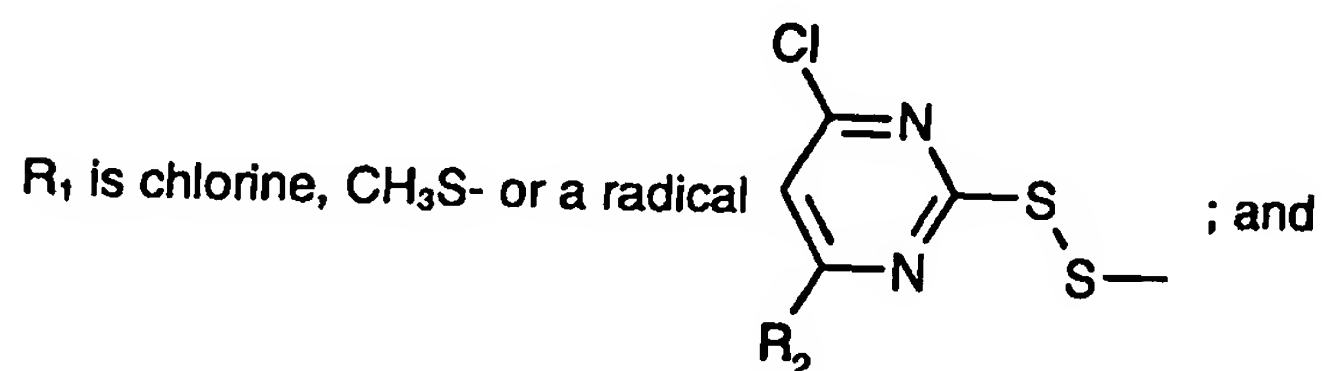
Also, chlorination with phosphorus oxychloride very often leads to thermally unstable intermediate stages, which impair safety of the production method.

Surprisingly, it has now been found that specifically substituted 4-chloropyrimidine derivatives can be easily produced particularly advantageously in high purity, economically and ecologically, avoiding the disadvantages of the described methods, from (thio)barbituric acid derivatives, by effecting chlorination or oxidation with a chlorination agent other than phosphorus chlorides, in the presence of catalysts in an inert reaction medium.

An object of the present invention is thus a method of producing 4-chloropyrimidine derivatives of formula I

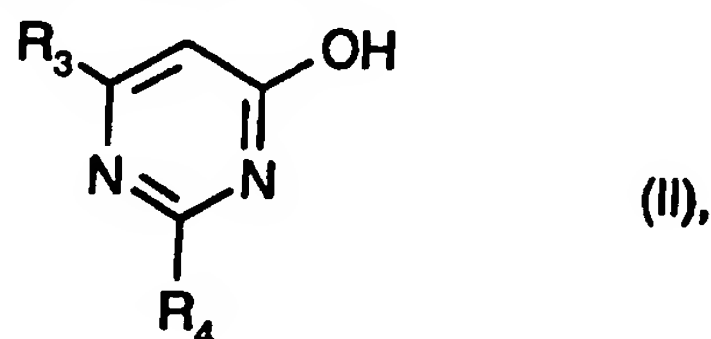


wherein



R<sub>2</sub> is chlorine or CH<sub>3</sub>O-,

by chlorination of a compound of formula II



wherein R<sub>3</sub> signifies OH or CH<sub>3</sub>O- and R<sub>4</sub> signifies OH, CH<sub>3</sub>S- or SH, in the presence of an inert solvent and at least one catalyst.

The chlorination agents suitable for chlorination of the compound of formula II are e.g. phosgene, diphosgene, chlorine and thionyl chloride. Phosgene and diphosgene are preferred in particular.

These chlorination agents are conveniently employed in an excess of 2 to 3 molar equivalents, based on the compound of formula II.

The chlorination reaction of the compound of formula II is effected by passing the chlorination agent into the reaction mixture at a reaction temperature of 0° to 200°C, depending on the reaction medium employed.

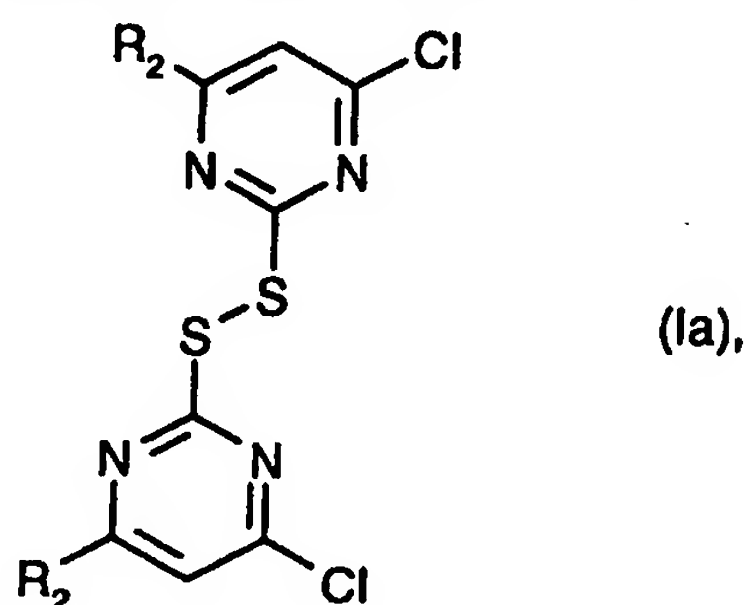
The inert organic solvents suitable for reacting the compound of formula II to the compound of formula I are, for example, aliphatic or aromatic hydrocarbons, such as dichloromethane, 1,1,2,2-tetrachloroethane, methylcyclohexane, benzene, toluene, the isomeric xylenes ortho-, meta- and para-xylene, chlorobenzene and the isomeric 1,2-dichlorobenzenes 1,2-, 1,3- and 1,4-dichlorobenzene; ethers such as tetrahydrofuran and dioxane, and mixtures of these solvents. Especially preferred are benzene, toluene, xylenes, chlorobenzene, dichlorobenzenes, methylcyclohexane, tetrahydrofuran and dioxane, as well as mixtures of these solvents. Particularly preferred are toluene, xylenes, chlorobenzene and dichlorobenzenes.

The reaction of the compound of formula II with the above-described chlorination agents advantageously takes place in the presence of at least one catalyst having the effect of accelerating and standardising the chlorination reaction. The catalyst in question may be phosphines and phosphine oxides, especially triphenylphosphine and triphenylphosphine oxide or copolymer-bound phosphines and phosphine oxides.

If desired, phase transfer catalysts may be additionally added as further catalysts, especially quaternary ammonium salts, e.g. tetraalkylammonium halides, for example tetrabutylammonium chloride or Aliquat as a dissolving intermediary between the (partly) dissolved educt of formula II and the chlorination agent triphenylphosphine dichloride formed *in situ*, with the effect of further accelerating the reaction. Further phase transfer catalysts suitable for the above chlorination reaction are described e.g. in Synthesis 1973, 441-456 and in Angew. Chem. Int. Ed. Engl. 13, 170-179 (1974).

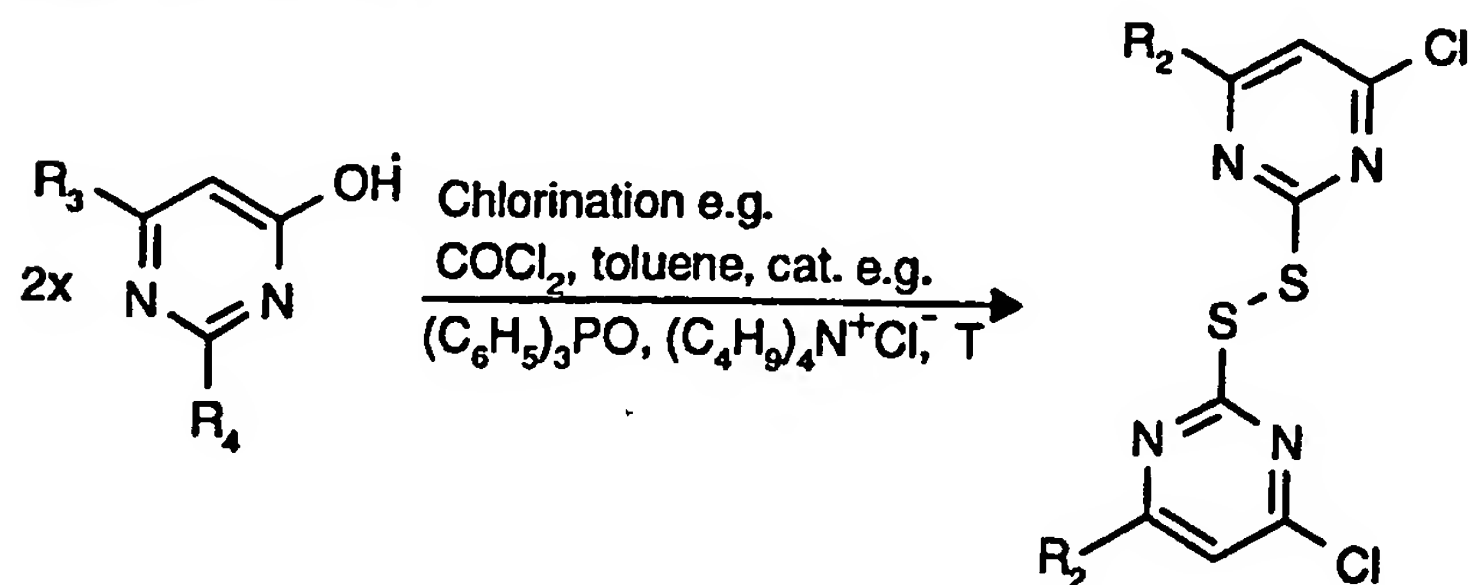
Each of these two types of catalyst is used in amounts of 1 to 10 mol%, especially 5 mol%, based on the compound of formula II.

If two mols of the compound of formula II, wherein  $R_3$  is OH or  $\text{CH}_3\text{O}-$  and  $R_4$  is SH, are used as the starting compound for the chlorination reaction according to the invention, then one mol of the 2-pyrimidinyl disulphide of formula Ia



wherein  $R_2$  is chlorine or  $\text{CH}_3\text{O}-$ , are obtained. Reaction scheme 1 illustrates this reaction.

#### Reaction scheme 1



II:  $R_3 = \text{OH}, \text{CH}_3\text{O}-$ ,  
 $R_4 = \text{SH}$

Ib:  $R_2 = \text{Cl}, \text{CH}_3\text{O}-$

The compound of formula Ib, in which  $R_2$  signifies  $\text{CH}_3\text{O}-$ , is new. It therefore likewise forms an object of the present invention.

In a preferred variant of the chlorination reaction according to the invention, a compound of formula II is placed in pure toluene, xylene, chlorobenzene or dichlorobenzene in the presence of 1 to 10 mol% of triphenylphosphine or triphenylphosphine oxide and 1 to 10 mol% of a quaternary ammonium salt, both based on the compound of formula II, at a reaction temperature of  $0^\circ$  to  $25^\circ\text{C}$ , this reaction mixture is heated until just below the reflux

temperature of the solvent used, and chlorinated at this temperature by passing in phosgene, diphosgene, chlorine or thionyl chloride until the compound of formula II has completely reacted. After cooling the reaction mixture, the crude product obtained can either be used directly for further reactions, or can be prepared in pure form by distilling the solvent and purifying in conventional manner, e.g. by recrystallisation. The yields are generally in the range of 20 to  $\geq 90\%$  of theory.

In an especially preferred variant of the chlorination reaction according to the invention, a compound of formula II, wherein  $R_3$  is OH or  $\text{CH}_3\text{O}-$  and  $R_4$  is  $\text{CH}_3\text{S}-$ , is placed in pure toluene, xylene, chlorobenzene or dichlorobenzene in the presence of 1 to 10 mol% of triphenylphosphine or triphenylphosphine oxide and 1 to 10 mol% of tetrabutylammonium chloride, both based on the compound of formula II, at a reaction temperature of  $0^\circ$  to  $25^\circ\text{C}$ , this reaction mixture is subsequently heated until just below the reflux temperature of the solvent used, and chlorinated at this temperature by passing in phosgene, diphosgene, chlorine or thionyl chloride until the compound of formula II has completely reacted.

The compounds of formula I which are preferably produced by the method according to the invention are bis-(4,6-dichloro-2-pyrimidinyl)-disulphide, bis-(4-chloro-6-methoxy-2-pyrimidinyl)-disulphide, 2-methylmercapto-4,6-dichloropyrimidine, 2-methylmercapto-4-chloro-6-methoxypyrimidine and 2,4,6-trichloropyrimidine, especially 2-methylmercapto-4,6-dichloropyrimidine and 2-methylmercapto-4-chloro-6-methoxypyrimidine.

The starting compounds of formula II, as well as all the chlorination agents and catalysts employed, are known or may be produced by known methods. For example, EP-A-0 529 631 describes the production of disodium thiobarbiturate and 2-(methylthio)-disodium barbiturate by reacting thiourea, malonic acid dimethyl ester and sodium methanolate, followed by methylation with methyl bromide. DE-OS-2 412 854 describes the production of 2-methylthio-4-hydroxy-6-methoxypyrimidine from 2-methylthio-4,6-dihydroxypyrimidine by means of methylation with dimethylsulphate (DMS) in the presence of a base, and 2-methylthio-4,6-dihydroxypyrimidine from thiobarbituric acid by means of methylation with DMS in the presence of a base.

The method according to the invention is distinguished from known methods in that



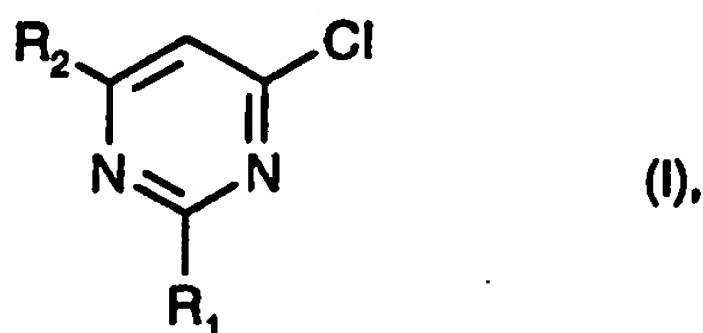
- 1) Instead of the conventional phosphorus (oxy)chlorides or phosphorus (oxy)chlorides in combination with chlorine or thionyl halides, other chlorination agents are used, and therefore no phosphates or phosphoric esters are obtained as waste material.
- 2) chlorination is effected in the presence of at least one catalyst, which thereby
  - a) accelerates the reaction and
  - b) standardises the chlorination reaction by reducing the amount of undesired by-products, and
- 3) the products are obtained in an inert reaction medium which is suitable for further reactions.

The advantages of the present process over the known processes are therefore:

- 1) it is particularly suitable for large-scale applications with substantially more favourable balance of waste e.g. in respect of phosphates.
- 2) it avoids the usage of complex separation and purification steps,
- 3) it is possible to further process the formed 4-chloropyrimidine derivatives of formula I in a one-pot process without changing the solvents and thereby reduce the solvent residues and the need for complex apparatus.
- 4) the process has higher thermal safety and
- 5) it is possible to use polymer-bound phosphines and phosphine oxides with simplified separation of these catalysts after the reaction has been carried out.

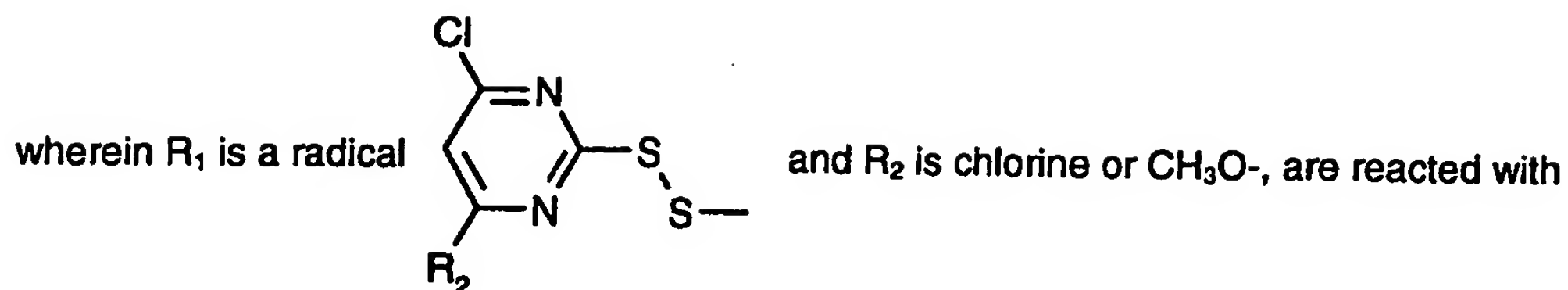
The 4-chloropyrimidine derivatives of formula I which are produced according to the invention are used especially as intermediates in the production of 7-[(4,6-dimethoxy-pyrimidin-2-yl)thio]-3-methylphthalide, as described for example in EP-B-0 447 506 .

In a first reaction step, therefore, the 4-chloropyrimidine intermediates of formula I which are produced according to the invention



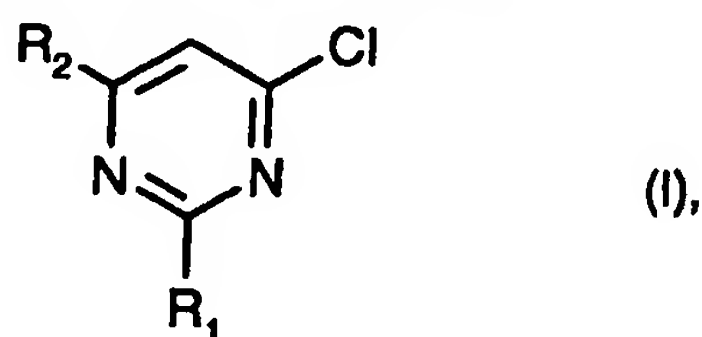


- 7 -



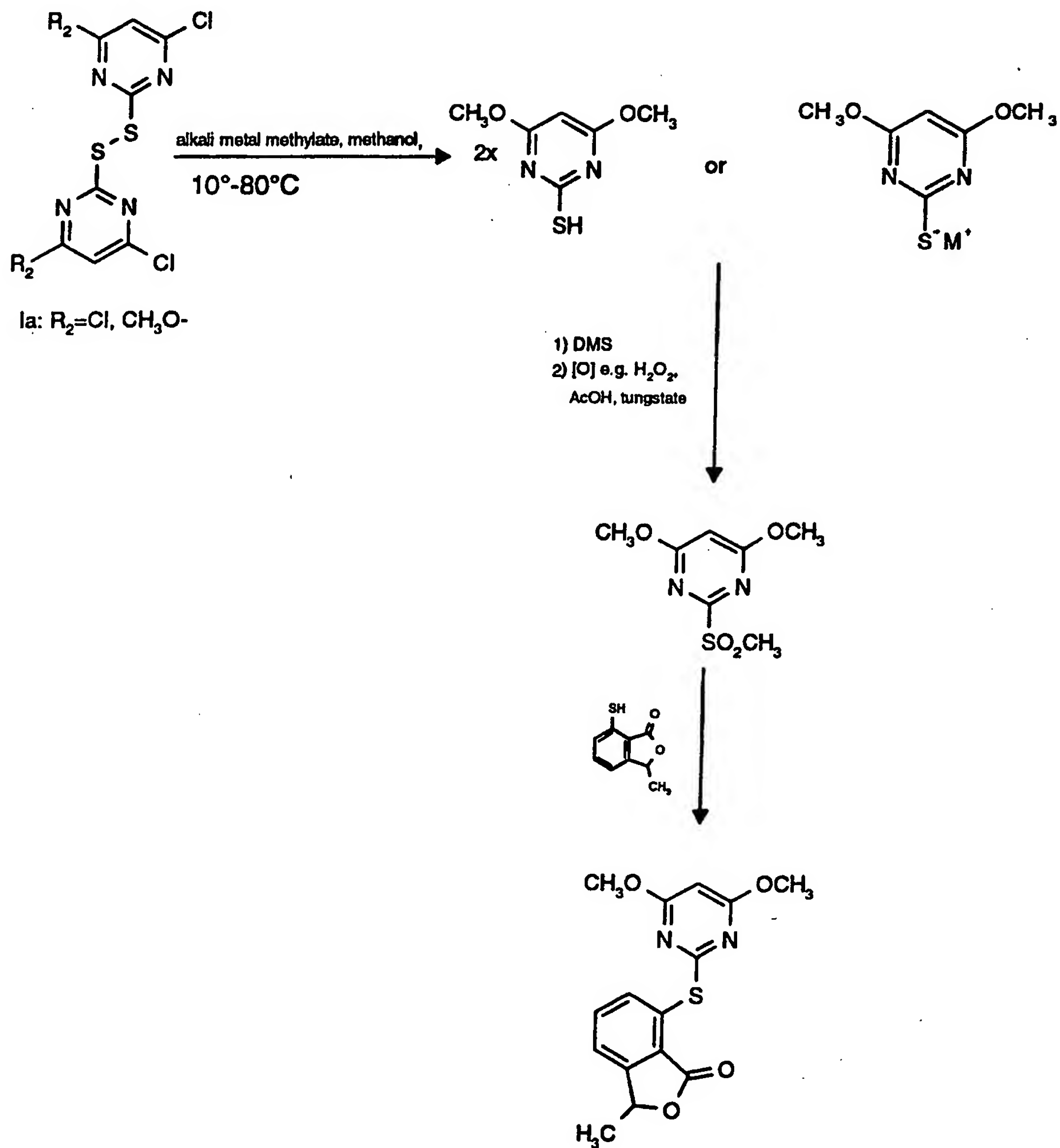
an excess of 2 to 6 molar equivalents of alkali metal methylate in methanol, based on the compound of formula I, and the obtained 4,6-dimethoxy-2-pyrimidinethiole or the alkali metal salts thereof is or are reacted firstly with a methylation agent such as dimethylsulphate (DMS), then with an oxidation agent such as peroxides, for example hydrogen peroxide, in acetic acid and in the presence of alkali metal tungstate, or chlorine, and the obtained 4,6-dimethoxy-2-(methylsulphonyl)pyrimidine is reacted with 7-mercapto-3-methylphthalide.

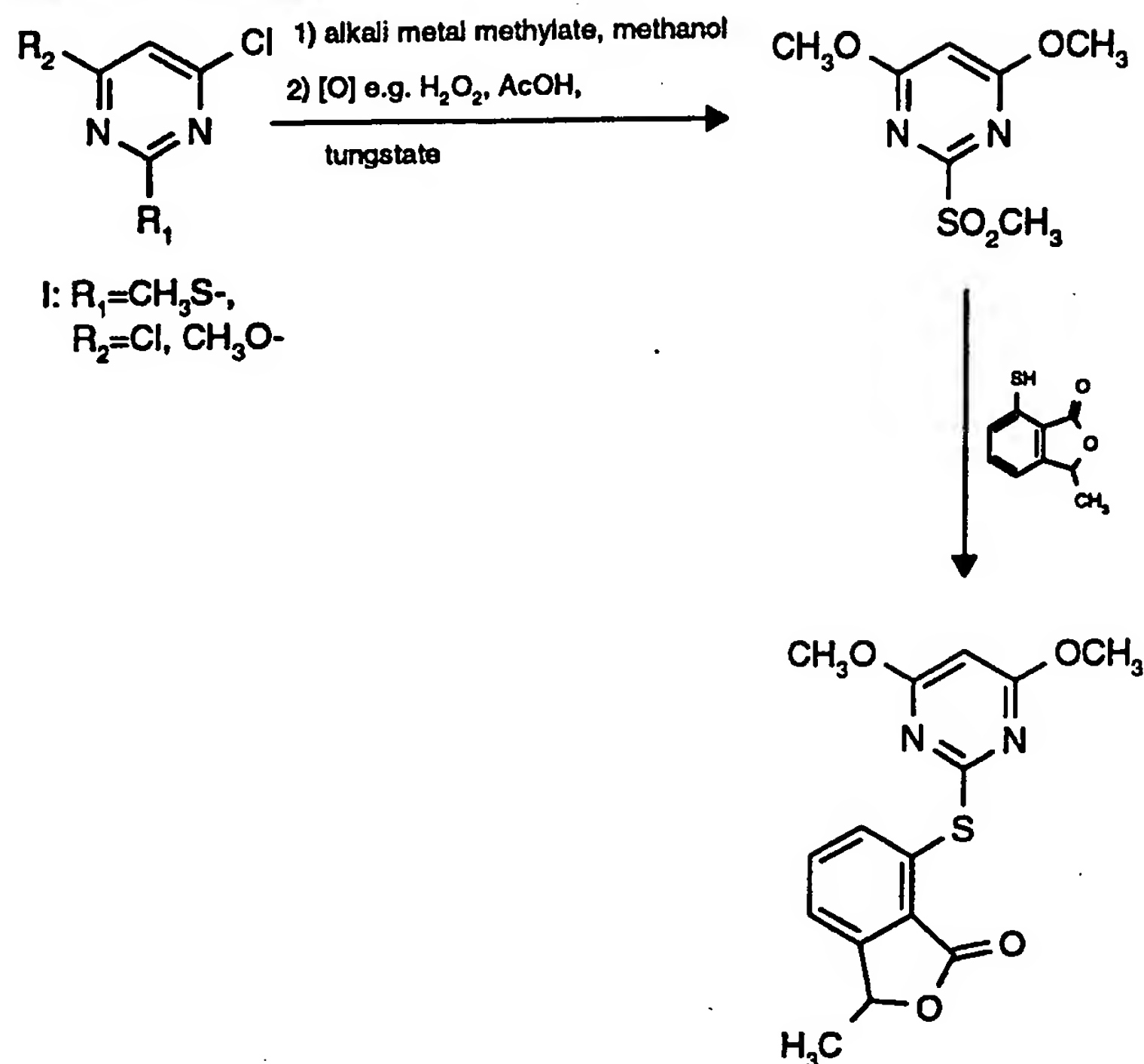
In a subsequent reaction step, therefore, the 4-chloropyrimidine intermediates of formula I which are produced according to the invention



wherein  $R_1$  is  $\text{CH}_3\text{S}-$  and  $R_2$  is chlorine or  $\text{CH}_3\text{O}-$ , are reacted with a small excess (ca. 5-10 mol%) of alkali metal methylate in methanol and subsequently with an oxidation agent such as peroxides, for example hydrogen peroxide in acetic acid, and in the presence of alkali metal tungstate, or chlorine, and the obtained 4,6-dimethoxy-2-(methylsulphonyl)pyrimidine is reacted with 7-mercapto-3-methylphthalide.

The above process variants for the production of 7-[(4,6-dimethoxypyrimidin-2-yl)thio]-3-methylnaphthalide are illustrated in the following reaction schemes 2 and 3.

Reaction scheme 2

Reaction scheme 3

Cleavage of the disulphide derivative of formula Ia to the 4,6-dimethoxy-2-pyrimidinethiole or to the alkali metal salt thereof, in which  $M^+$  is an alkali metal ion such as a sodium or potassium ion, in reaction scheme 2, advantageously takes place with an excess of 2 to 6 molar equivalents of alkali metal methylate, such as sodium methylate in methanol at temperatures of 10° to 80°C.

The methylation of 4,6-dimethoxy-2-pyrimidinethiole or the alkali metal salt thereof with dimethylsulphate (DMS) to the intermediate 4,6-dimethoxy-2-methylthiopyrimidine (reaction scheme 2) conveniently takes place in an aqueous-basic medium, optionally in the presence of a polar organic solvent, such as alcohols, at temperatures of 0° to 40°C. The subsequent oxidation, e.g. with hydrogen peroxide in above solvents or in organic acids, such as alkanecarboxylic acids, for example acetic acid, and optionally in the presence of alkali metal tungstate, such as sodium tungstate, or with chlorine gas, yields the 4,6-dimethoxy-2-methylsulphonylpyrimidine. Methylation and oxidation reactions of this kind are described for example in DE-A-2 412 854, DE-A-3 324 399, EP-A-0 033 195, Z. Chem. 17(392), 63 (1977), Chem. Soc. 16(6), 489 (1995) and J. Org. Chem. 26, 792 (1961).

The subsequent reaction of the formed 4,6-dimethoxy-2-(methylsulphonyl)pyrimidine with 7-mercapto-3-methylphthalide (reaction scheme 2) conveniently takes place in an inert organic solvent such as ethers, ketones, nitriles and amides, for example tetrahydrofuran, butanone, acetonitrile and N,N-dimethylformamide, at temperatures of 0° to 160°C. Substitution reactions of this kind are described e.g. in EP-A-0 447 506.

According to reaction scheme 3, the 4-chloropyrimidine derivative of formula I is firstly reacted with alkali metal methylate in methanol, then with an oxidation agent, and the 4,6-dimethoxy-2-(methylsulphonyl)pyrimidine obtained undergoes a substitution reaction with the 7-mercapto-3-methylphthalide.

The first reaction step according to reaction scheme 3, namely the reaction of the compound of formula I with an alkali metal methylate in methanol is effected analogously to the manner described e.g. in J. Org. Chem. 27, 1462 (1962), EP-A-0 547 411 and J. Am. Chem. Soc. 76, 2899 (1954). The subsequent oxidation of the 4,6-dimethoxy-2-methylthiopyrimidine thus formed, and the substitution reaction in the presence of 7-mercapto-3-methylphthalide, are effected analogously to the manner already described for reaction scheme 2.

The following examples further illustrate the method according to the invention.

Example P1: Preparation of 4,6-dichloro-2-methylthiopyrimidine

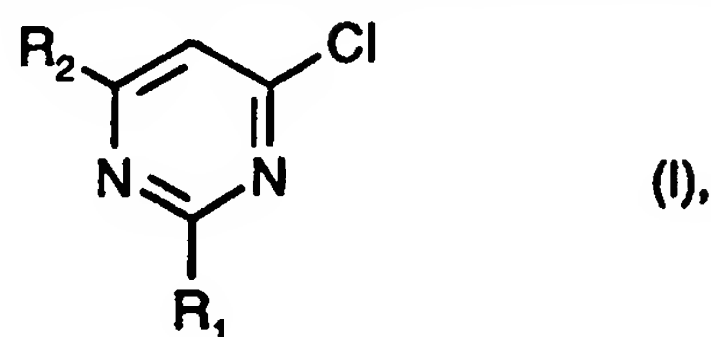
8.5 g (1 molar equivalent) of 2-methylthiobarbituric acid is placed in 150 g of xylene and mixed with 1.3 g (5 mol%) of triphenylphosphine oxide and additionally with 1.3 g (5 mol%) of tetrabutylammonium chloride. Afterwards, heating is effected until just below the reflux temperature, and 19.8 g of phosgene passed in, until reaction of the educt is complete (ca. 2 molar equivalents). The phosgene is removed from the reaction mass by passing in nitrogen, and the mass is subsequently cooled. The organic phase is extracted once with water and the salts removed, the solvent is distilled off and the intermediate product 4,6-dichloro-2-methylthiopyrimidine is obtained as a yellow to brown oil. Upon cooling, the desired title compound crystallises. Yield 80% of theory.

**Example P2: Preparation of 4,6-dimethoxy-2-(methylsulphonyl)pyrimidine**

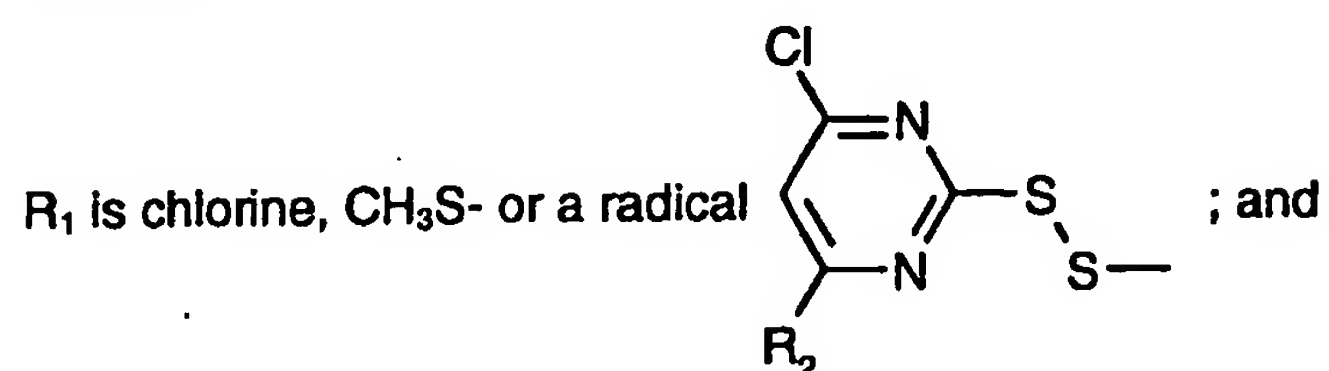
8.5 g (1 molar equivalent) of 2-methylthiobarbituric acid is placed in 150 g of xylene and mixed with 1.3 g (5 mol%) of triphenylphosphine oxide and additionally with 1.3 g (5 mol%) of tetrabutylammonium chloride. Afterwards, heating is effected until just below the reflux temperature, and 19.8 g of phosgene passed in, until reaction of the educt is complete (ca. 2 molar equivalents). The phosgene is removed from the reaction mass by passing in nitrogen, and the mass is subsequently cooled. The organic phase is extracted once with water and the salts removed. The solvent is dried by evaporating under vacuum for a short time, and reacted with 22.5 g (2.5 molar equivalents) of sodium methylate (30%) at 50°C to form 4,6-dimethoxy-2-methylthiopyrimidine. Subsequently, 0.83 g (5 mol%) of sodium tungstate and 0.7 g (5 mol%) of tetrabutylammonium chloride are added to the reaction mixture obtained, and mixed at 85°C with 2 molar equivalents of hydrogen peroxide. The product precipitates during oxidation and may be isolated from the reaction mixture by filtration at 0°C.

What we claim is:

1. Method of producing 4-chloropyrimidine derivatives of formula I

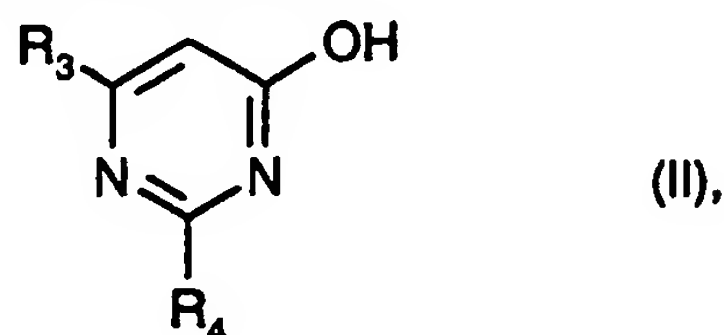


wherein



R<sub>2</sub> is chlorine or CH<sub>3</sub>O-,

by chlorination of a compound of formula II



wherein R<sub>3</sub> signifies OH or CH<sub>3</sub>O- and R<sub>4</sub> signifies OH, CH<sub>3</sub>S- or SH, in the presence of an inert solvent and at least one catalyst.

2. Method according to claim 1, in which phosgene, diphosgene, chlorine or thionyl chloride is used as the chlorination agent for chlorination.

3. Method according to claim 2, in which the chlorination agent is used in an excess of 2 to 3 molar equivalents, based on the compound of formula II.

4. Method according to claim 2, in which the chlorination agent is passed into the reaction mixture at a reaction temperature of 0° to 200°C.

5. Method according to claim 1, in which aliphatic or aromatic hydrocarbons, ethers or mixtures of these solvents are used as the inert solvents.

6. Method according to claim 5, in which dichloromethane, 1,1,2,2-tetrachloroethane, benzene, toluene, xylenes, chlorobenzene, dichlorobenzenes, methyl cyclohexane, tetrahydrofuran or dioxane, or mixtures of these solvents, are used as the solvents.

7. Method according to claim 1, in which phosphines or phosphine oxides, especially triphenylphosphine or triphenylphosphine oxide, or copolymer-bound phosphines or phosphine oxides, are used as the catalysts.

8. Method according to claim 7, in which phase transfer catalysts are additionally employed, especially quaternary ammonium salts.

9. Method according to claim 8, in which the catalysts are each used in amounts of 1 to 10 mol%, especially 5 mol%, based on the compound of formula II.

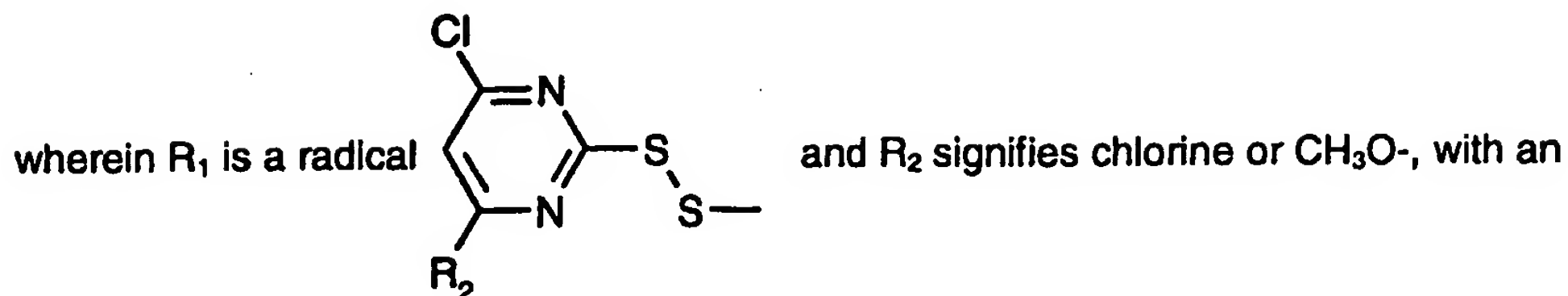
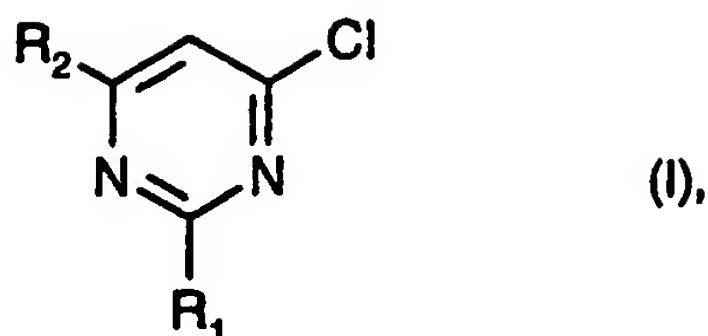
10. Method according to claim 1, in which the compound of formula II, wherein  $R_3$  is OH or  $CH_3O-$  and  $R_4$  is  $CH_3S-$ , is placed in pure toluene, xylene, chlorobenzene or dichlorobenzene in the presence of 1 to 10 mol% of triphenylphosphine or triphenylphosphine oxide and 1 to 10 mol% of tetrabutylammonium chloride, both based on the compound of formula II, at a reaction temperature of 0° to 25°C, and this reaction mixture is subsequently heated until just below the reflux temperature of the solvent used, and chlorinated by passing in phosgene, diphosgene, chlorine or thionyl chloride.

11. Method according to claim 1 for the production of bis-(4,6-dichloro-2-pyrimidinyl)-disulphide, bis-(4-chloro-6-methoxy-2-pyrimidinyl)-disulphide, 2-methylmercapto-4,6-dichloro-pyrimidine, 2-methylmercapto-4-chloro-6-methoxy-pyrimidine and 2,4,6-trichloropyrimidine.

12. Use of the 4-chloropyrimidine derivatives produced according to claim 1 as intermediates in the production of 7-[(4,6-dimethoxy-pyrimidin-2-yl)thio]-3-methylphthalide by reacting the compound of formula I

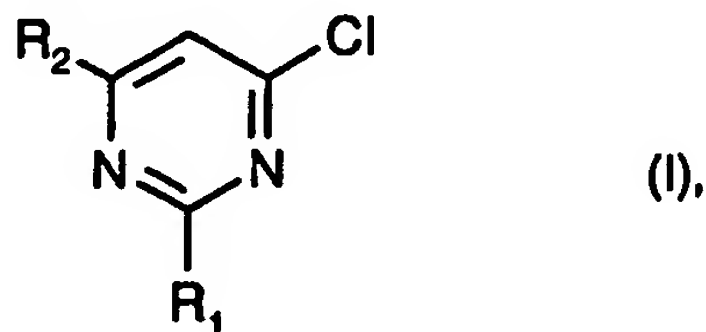


- 14 -



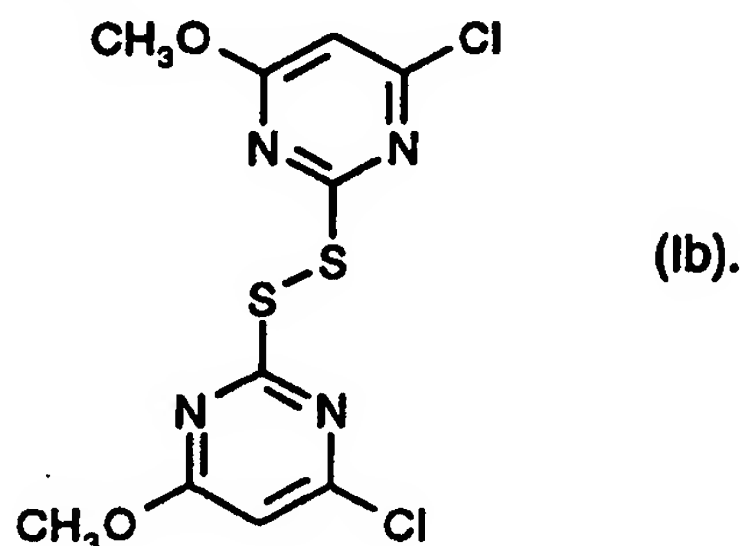
excess of 2 to 6 molar equivalents of alkali metal methylate in methanol, based on the compound of formula I, and further reacting the obtained 4,6-dimethoxy-2-pyrimidinethiole or the alkali metal salts thereof with a methylation agent, then with an oxidation agent and the obtained 4,6-dimethoxy-2-(methylsulphonyl)pyrimidine is reacted with 7-mercapto-3-methylphthalide.

13. Use of the 4-chloropyrimidine derivatives produced according to claim 1 as intermediates in the production of 7-[(4,6-dimethoxy-pyrimidin-2-yl)thio]-3-methylphthalide by reacting the compound of formula I



wherein R<sub>1</sub> signifies CH<sub>3</sub>S- and R<sub>2</sub> signifies chlorine or CH<sub>3</sub>O-, with a small excess of alkali metal methylate in methanol, with subsequent oxidation and further reacting the obtained 4,6-dimethoxy-2-(methylsulphonyl)pyrimidine with 7-mercapto-3-methylphthalide.

14. Compound of formula Ib



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 00/00873

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/30 C07D239/38 C07D239/56 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 095 637 A (BAYER) 7 December 1983 (1983-12-07) the whole document ---	1-7
X	WO 95 29166 A (ZENECA) 2 November 1995 (1995-11-02) page 1 -page 6 ---	1-6
A	C.W. TODD: "SULFILIMINES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 65, 1943, pages 350-4, XP002141178 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 354 --- -/--	1-4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

27 June 2000

Date of mailing of the international search report

11/07/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 00/00873

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 05781 A (R. MAAG) 2 May 1991 (1991-05-02) example 1; tables -----	12, 13

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 00/00873

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 095637	A	07-12-1983	DE 3220105 A	01-12-1983
WO 9529166	A	02-11-1995	BR 9507481 A	12-08-1997
			CA 2182522 A	02-11-1995
			CN 1146766 A	02-04-1997
			CZ 9603126 A	15-01-1997
			EP 0757678 A	12-02-1997
			HU 74713 A	28-02-1997
			IL 113143 A	24-09-1998
			JP 9512263 T	09-12-1997
			PL 317019 A	03-03-1997
			SK 137196 A	07-05-1997
			US 5750694 A	12-05-1998
WO 9105781	A	02-05-1991	AU 635069 B	11-03-1993
			AU 6347190 A	16-05-1991
			BR 9006950 A	10-12-1991
			CA 2044135 A	13-04-1991
			DE 59007567 D	01-12-1994
			EP 0447506 A	25-09-1991
			ES 2063374 T	01-01-1995
			IL 95937 A	26-08-1994
			JP 2990377 B	13-12-1999
			JP 4504265 T	30-07-1992
			KR 172947 B	01-02-1999
			LT 1847 A, B	25-08-1995
			LV 10443 A	20-02-1995
			LV 10443 B	20-04-1996
			SU 1838310 A	30-08-1993
			US 5332717 A	26-07-1994
			US 5428002 A	27-06-1995